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Hematopoietic Cell Transplantation in Patients with Systolic Heart Failure: Can It be Done?

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Introduction: Hematopoietic cell transplantation (HCT) is a potential cure for certain hematologic malignancies. However due to risks of complications and mortality, this treatment option is limited to patients with minimal comorbidities. There are few data on patients with systolic heart failure undergoing HCT. We performed a case control study evaluating the impact of pre-HCT systolic heart failure on outcomes.

Methods: We studied 48 subjects with systolic heart failure defined as left-ventricular ejection fraction (LVEF) <50% and 48 controls (matched by age, gender, conditioning regimen, and number of transplanted units) with LVEF >= 50% undergoing HCT at the University of Minnesota between 2002-2012. Treatment complications and mortality at 100 days, as well as overall survival (OS) after HCT at 100 days, 12 months and 24 months were determined including use of beta-blockers and angiotensin converting enzyme (ACE) inhibitors.

Results: The median pre-transplant age was 51.9 (19.1-69.2) years in the study group and 54.5 (20.7-72.5) years in the controls; each including 31 males (63.3%) and 18 females (36.7%). In both groups, 9 patients (18.8%) received myeloablative conditioning regimen and 39 (81.3%) had reduced intensity conditioning. The median LVEF was 45% (27.5-49%) for the study group and 60% (50-69%) for the control. Beta-blocker use at the time of HCT (32.7% in the study group vs. 4.1% in the control; $p<0.01$) and ACE-inhibitor use (30.6% in the study group vs. 6.1% in the control; $p<0.01$) were more common in the study group compared to the control group. Treatment related mortality (TRM) at day 100 was identical with a cumulative incidence of 7 of 48 (15%) in the study (RR 15%, 95% CI 5-24%) and 7 of 48 (15%) in the control (RR 15%, 95% CI 5-25%) ($p=0.88$). There was no significant difference in the 2-year OS between the study group (n=26, 54%, CI 39-67%) compared to the control group (n=29, 60%, CI 45-72%) ($p= 0.43$). An LVEF >= 43% was a threshold for improved OS at 1 year (HR 0.36, 95% CI 15-87%; $p=0.02$). There was no significant increase in the incidence of minor (non-life-threatening) cardiac complications (12.2% in the study vs. 8.2% in the control, $p=0.50$) or serious (life-threatening or fatal) cardiac complications (4.1% in the study group vs. 2.0% in the control, $p=0.56$) between groups. The use of beta-blockers (HR 0.43, 95% CI 20-89%, $p=0.02$) and ACE-inhibitors (HR 0.34, 95% CI 16-70%, $p<0.01$) at the time of HCT was associated with improved OS at 1 year.

Conclusion: Our results suggest that patients with reduced systolic heart function, particularly with an EF >= 43%, should not be excluded from HCT. However, a LVEF < 43% was associated with reduced OS at 1 year. Additionally, beta-blockers and ACE-inhibitors use should be part of the treatment plan for this population when undergoing HCT.

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Extended Follow-up of Myeloablative, HLA-Matched Allogeneic BMT with High-Dose, Post-Transplantation Cyclophosphamide (PTCy) As Sole GVHD Prophylaxis: Favorable Outcomes Despite Low Incidence of Chronic GVHD

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Introduction: High-dose, PTCy is an effective strategy for GVHD prevention after allogeneic blood or marrow transplantation (alloBMT), but the impact of PTCy on long-term outcomes, particularly relapse, has not been assessed. Here we report outcomes for 291 consecutive adult patients at Johns Hopkins treated with PTCy as sole GVHD prophylaxis.

Methods: All adult patients treated with this approach from its commencement in 2004 through 2011 were included. Data were locked on June 30, 2013. Median follow-up was 3.7 years (range 0.3-8.3) for surviving patients. Allograft donors were HLA-matched-related for 60% and HLA-matched-unrelated for 40%. All allografts were T cell replete and bone marrow derived in all but one who received peripheral blood stem cells. Myeloablative conditioning (MAC) was busulfan(Bu)/Cy in 248 patients (85%), Bu/fludarabine in 42 (14%), and Cy/total body irradiation in 1 (0.3%).

Median patient age was 49 years (range 18-66), and median HCT-CI score was 2 (range 0-12) with 39% having a score of $\geq$3. At the time of transplant, 31% of patients were not in remission and an additional 28% had minimal residual disease. Diseases included 138 AML (47%), 43 ALL (15%), 28 MDS (10%), 31 non-Hodgkin lymphomas (11%), 24 CML (8%), 13 Hodgkin lymphoma (4%), 9 multiple myeloma (3%), and 5 other diseases (2%). High-risk disease characteristics of AML patients included adverse cytogenetics by the refined MRC criteria in 58 (42%), Flt3/ITD positivity in 37 (27%), and secondary from antecedent hematologic disorder in 51 (37%). Forty-four percent of ALL patients were Philadelphia chromosome (Ph) positive.

Results: Primary graft failure occurred in 9 patients (3%). By competing-risk analysis, the cumulative incidences (CI) of non-relapse mortality at 1 and 3 years were 17% and 18%, respectively. Venocclusive disease occurred in 17 patients (6%) and was fatal in 4 patients (1%).

The CIs of grades II-IV and III-IV acute GVHD were 44% and 14%, respectively, and acute GVHD was the cause of death in 6 patients (2%). The CIs of grades III-IV acute GVHD were not different between matched-related or matched-unrelated alloBMT. The total CI of chronic GVHD was 11% (8% for matched-related and 16% for matched-unrelated, p=0.03).

The CI of relapse at 3 years for all patients was 39% (37% AML, 33% ALL, 40% MDS). The 3-year disease-free survival (DFS) probability for all patients was 42% (43% AML, 55% ALL, 53% MDS). The 3-year overall survival (OS) probability for all patients was 58% (53% AML, 74% ALL, 67% MDS). DFS and OS were similar regardless of donor relatedness. A statistically significant impact of Flt3/ITD in AML or Ph+ in ALL on DFS or OS was not detected.

Conclusion: The use of PTCy as sole GVHD prophylaxis after MAC HLA-matched alloBMT is associated with a favorable toxicity profile and affords long-term disease control for a large subset of patients with poor-risk hematologic malignancies in the absence of chronic GVHD.